An integrated genetic and physical map of chromosome 19 as a resource for identification of disease genes. A.S. Olsen, L.K. Ashworth, J.E. Lamerdin, E.Garcia, P. McCready, L.A. Gordon, G. Lennon, A.V. Carrano, and H.Mohrenweiser, Human Genome Center, Biology and Biotechnology Research Program, Lawrence Livermore National Laboratory, Livermore, CA 94550.

Chromosome 19 is approximately 65 Mb, or 2% of the haploid genome. It is the most GC-rich chromosome, suggesting an especially high gene density. A variety of uncloned disease genes have been reported to map to this chromosome, including several neurological diseases (CICA, CADASIL, EA2, and MHP1) in p13, a congenital nephrotic syndrome (NPHS1) in q13.1, a connective tissue disorder (EXT3) in p13, a retinal dystrophy (CORD2) in q13, an orofacial cleft (OFC3) in q13, and an autosomal deafness (DFNA4) in q13. We have developed a cosmid-based physical map that covers over 90% of the non-centromeric portion of chromosome 19. The order of, and distance between, the constituent contigs have been determined by high-resolution FISH to decondensed sperm pronuclei, resulting in a "metric" map with known distances. Over 150 polymorphic markers have been integrated into the physical map. There is good correspondence between the genetic and physical order of these markers, but some striking differences in relative genetic and physical distances. While the overall ratio of genetic to physical distance for chromosome 19 is about 2:1(cM:Mb), a several-fold higher ratio is found for markers in the telomeric regions. The integrated physical map provides the cloned material critical for identifying disease genes localized relative to genetic markers. Complete digest EcoRI maps have been constructed for contigs spanning about 45 Mb (>80%) of the non-centromeric portion of the chromosome. The map includes 21 Mb of restriction mapped contigs greater than 200 kb (average size 390 kb), which provide ideal substrates for large-scale genomic sequencing. A 1-Mb contig spanning the NPHS1 candidate region is currently being sequenced in an effort to identify new genes in this region.

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